X Workshop Nazionale

Innovazione e Ricerca per la Pratica Clinica

TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI

Up date sul paziente pediatrico

Firenze, 14 gennaio 2020

Giuseppe Indolfi

UNIVERSITÀ DEGLI STUDI FIRENZE

Penta Child Health Research

MEYER Azienda Ospedaliero-Universitaria

Up date sul paziente pediatrico

- **Treatment options**
- **Uptake of treatment and correlated challenges**
- **Efficacy and safety**
- **Microelimination**

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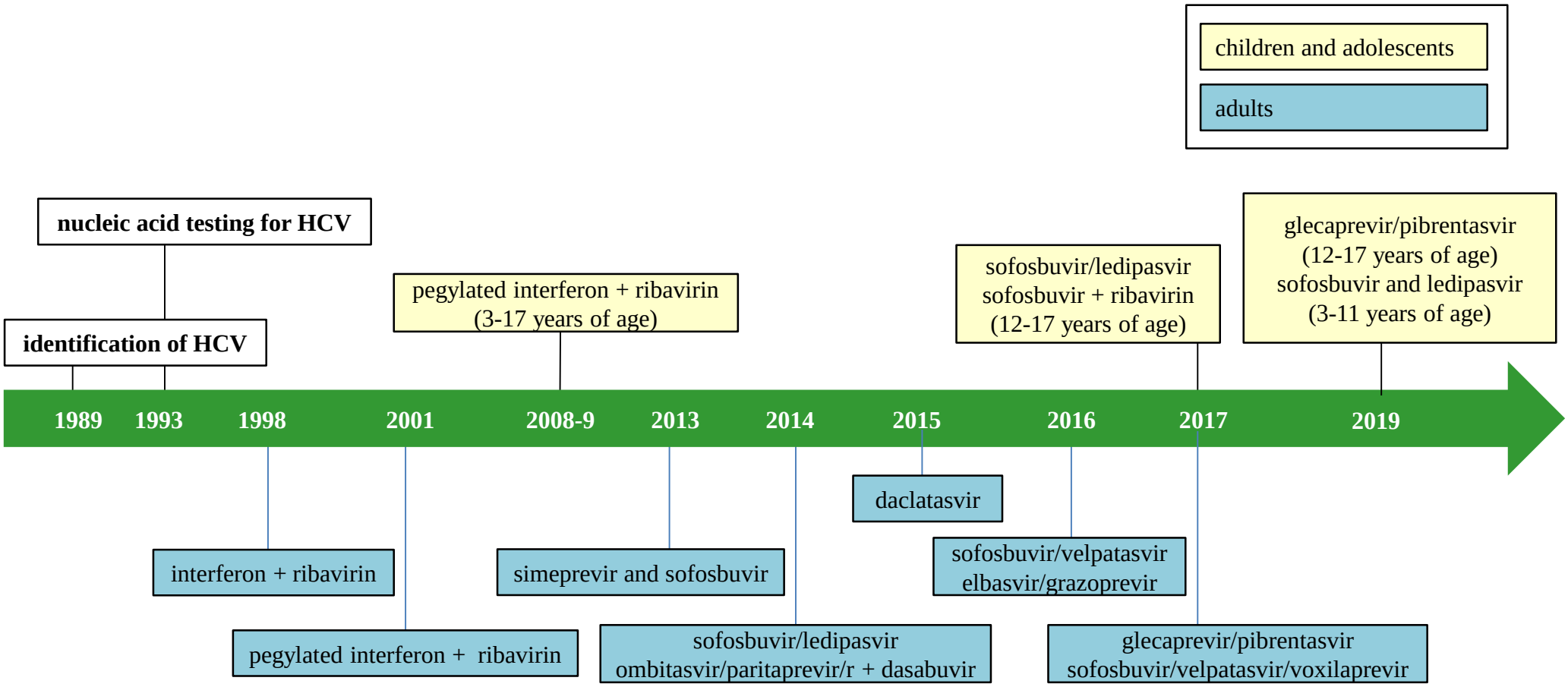


Indolfi, Hepatology Comm 2018

DAA regimens approved for treatment of chronic HCV infection in children and adolescents

Regimen	Genotype (GT) & duration of Treatment	Formulations	Doses
sofosbuvir/ledipasvir	- GT 1, 4, 5, 6: 12 weeks - GT 1, treatment-experienced, cirrhosis: 24 weeks	- tablet (fixed-dose combination, FDC) 400/90 mg; - tablet (FDC) 100/22.5 mg - packet of granules 50/11.25 mg	- 12-17 years: 400/90 mg/day - 6-11 years: 200/45 mg/day - 3-5 years: 200/45 mg/day if ≥17 kg; 150/33.75 mg/day if <17 kg
sofosbuvir + ribavirin	- GT 2: 12 weeks - GT 3: 24 weeks	sofosbuvir - tablet 400 mg - tablet 100 mg - capsules 50 mg containing granules	sofosbuvir - 12-17 years: 400 mg/day - 6-11 years: 200 mg/day - 3-5 years: 200 if ≥17 kg; 150 mg/day if <17 kg ribavirin - 15 mg/Kg/day in 2 divided doses
glecaprevir/pibrentasvir	- all GTs: 8 weeks - all GTs, cirrhosis: 12 weeks - GT 3 treatment-experienced: 16 weeks	tablet (FDC) 100/40 mg/day	- 12-17 years: 300/120 mg/day

Indolfi & Giannini, Liver International 2020

PENTA-Hep Survey

Results

Would you use direct-acting antivirals* active against HCV if available, for children aged

	Yes	No	Maybe
3-5 years	**15 (42%)**	13 (36%)	8 (22%)
6-10 years	**28 (78%)**	7 (19%)	1 (3%)
11-18 years	**34 (94%)**	2 (6%)	0 (0%)

*survey distributed in 2017

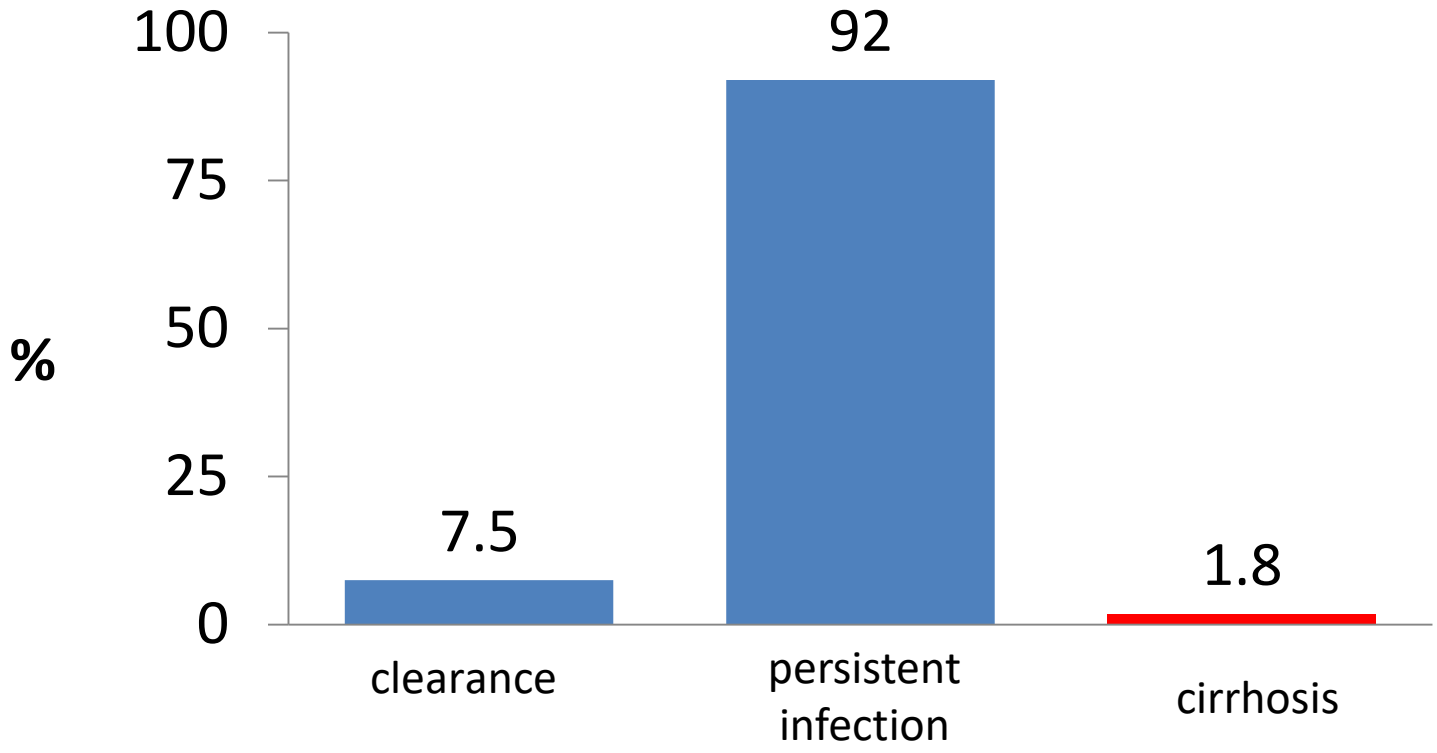
Indolfi on behalf of the PENTAHep Study Group, J Viral Hep 2019

Penta Child Health Research

Hepatitis C in Children

Natural history of the infection

- **504 children with hepatitis C**
- **follow up: 10 years**



Bortolotti F, Gastroenterology 2008

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❖ *Clinical practice guidelines counsel clinical practitioners providing evidence or expert-based recommendations for the optimal diagnosis, management or treatment of a disease and are invaluable to improving practice standards*

❖ *Lack of clarity and specificity with their recommendations impede their adoption into clinical practice and decrease their implementation*

DAA regimens approved for treatment of chronic HCV infection in children and adolescents

Regimen	US Food and Drug Administration-specific approval	European Medicines Agency-specific approval
Sofosbuvir/ledipasvir	- The dose indicated for use in adolescents 12-17 years of age can be used independently of the age of the patient for children weighing ≥ 35 kg	- Approved for use in adolescents >12 years without any specific weigh indication - GT 3: 24 weeks with ribavirin - GT 1, treatment-naïve and HCV RNA < $6x10^6$: 8 weeks Not yet approved for children < 12 years of age
Sofosbuvir + ribavirin	- The sofosbuvir dose indicated for use in adolescents 12-17 years of age can be used independently of the age of the patient for children weighing ≥ 35 kg	- Approved for use in adolescents > 12 years without any specific weight indication Not yet approved for children < 12 years of age
Glecaprevir/pibrentasvir	- The dose indicated for use in adolescents 12-17 years of age can be used independently of the age of the patient for children weighing ≥ 45 kg	- Approved for use in adolescents > 12 years without any specific weight indication

Indolfi for FISPGHAN, JPGN 2020

Recommendations for treatment with DAA of adolescents with chronic HCV infection

Document issued by	Recommendation	Level of evidence
WHO	Treatment should be offered to all individuals diagnosed with HCV infection who are 12 years of age irrespective of disease stage	Strong recommendation, moderate evidence
EASL	Adolescents without cirrhosis or with compensated (Child-Pugh A) cirrhosis should be treated	Strong recommendation, moderate evidence for HCV genotype 1 and 4 infection and weak recommendation, low evidence for HCV genotype 2 and 3 infection
AASLD	If direct-acting antivirals are available, treatment is recommended for all infected children older than 3 years	Strong recommendation, moderate evidence
Swedish Consensus Group	Treatment can be given from 12 years of age	Not reported
ESPGHAN	All children with chronic HCV infection are considered for therapy	Strong recommendation, high quality of evidence

Indolfi for FISPGHAN, JPGN 2020

Recommendations for treatment with DAA of children (3 - 11 years) with chronic HCV infection

Document	Recommendation	Level of evidence
WHO	Defer treatment to 12 years of age	Conditional recommendation, very low quality of evidence
EASL	Treatment should be deferred until direct-acting antivirals are approved for this age group	Strong recommendation, moderate evidence
AASLD	Treatment of children aged 3 to 11 years with chronic hepatitis C should be deferred until interferon-free regimens are available	Consensus opinion of experts, case studies, or standard of care; conflicting evidence. Three direct-acting antivirals regimen now approved in this age group since this publication
Swedish Consensus Group	Not provided	--
ESPGHAN	Treatment can be generally deferred in age-cohorts where combined pegylated interferon and ribavirin is the only treatment option	Strong recommendation, high evidence

Indolfi for FISPGHAN, JPGN 2020

Recommendations for treatment with DAA of children (3 - 11 years) with chronic HCV infection

Genotype 1, 4, 5 and 6 treatment-naive without cirrhosis or with compensated cirrhosis, or treatment-experienced without cirrhosis	Genotype 1, treatment-experienced with compensated cirrhosis	Genotype 2 treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis	Genotype 3 treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis	Genotype 4, 5, 6 WHO treatment-experienced with compensated cirrhosis
Sofosbuvir/ledipasvir (400/90 mg), once daily for 12 weeks (WHO, EASL, AASLD, SCG, ESPGHAN)	Sofosbuvir/ledipasvir (400/90 mg), once daily for 12 weeks (EASL) or for 24 weeks (AASLD, WHO and ESPGHAN)	Sofosbuvir + ribavirin (400 mg + weight-based ribavirin), once daily for 12 weeks (WHO, SCG and ESPGHAN)	Sofosbuvir + ribavirin (400 mg + weight-based ribavirin), once daily for 24 weeks (WHO, SCG and ESPGHAN)	Sofosbuvir/ledipasvir (400/90 mg), once daily for 12 weeks (AASLD, EASL) or for 24 weeks (WHO)
		EASL other regimens approved for adults, with caution pending more safety data in this population The SCG medical consensus suggests sofosbuvir/velpatasvir for 12 weeks as an alternative although not yet formally approved		

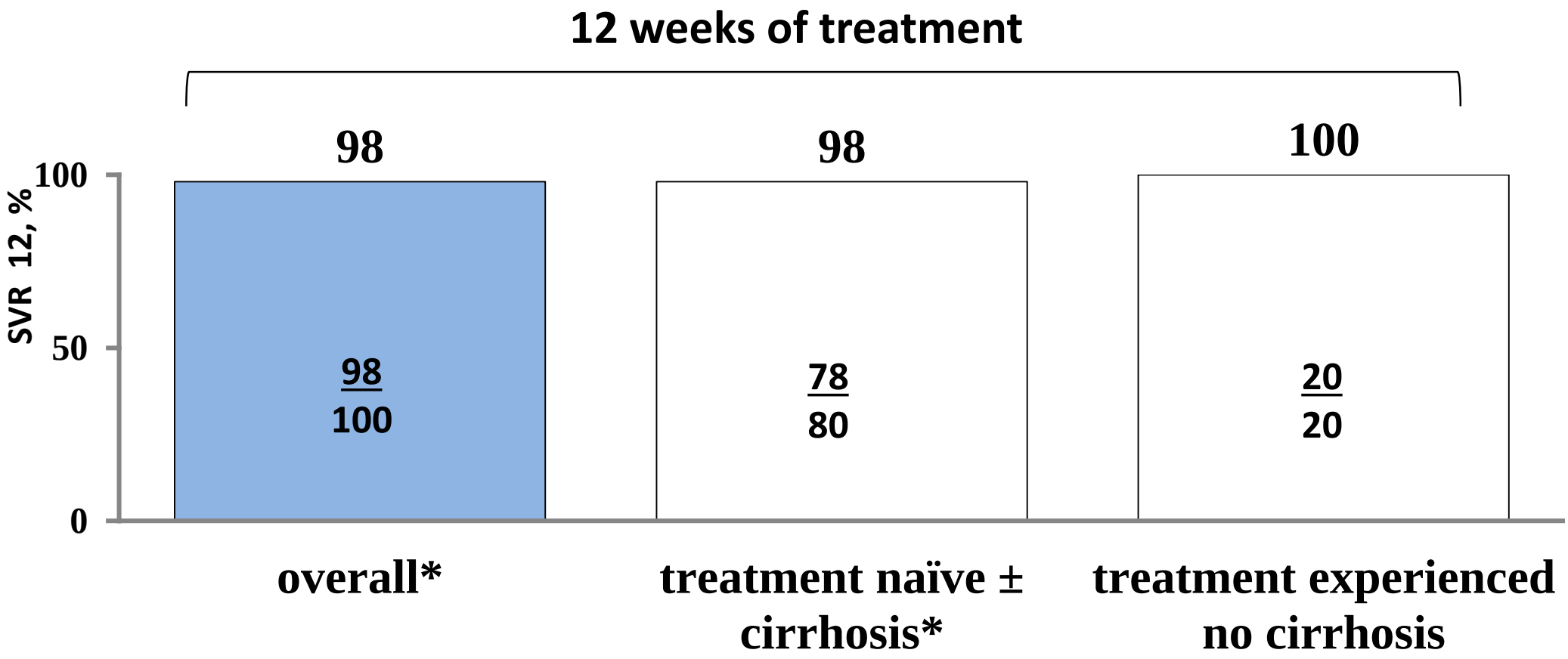
Indolfi for FISPGHAN, JPGN 2020

Sofosbuvir(nNS5B) / ledipasvir(NS5A) (FDC)

EMA FDA

NCT 02249182, industry-driven trial

12-17 years, GT1, treatment-naïve and experienced (n 20)



***1 discontinued the treatment; 1 achieved ETR and was lost to follow-up**

Sofosbuvir/ledipasvir (400/90 mg QD) FDC

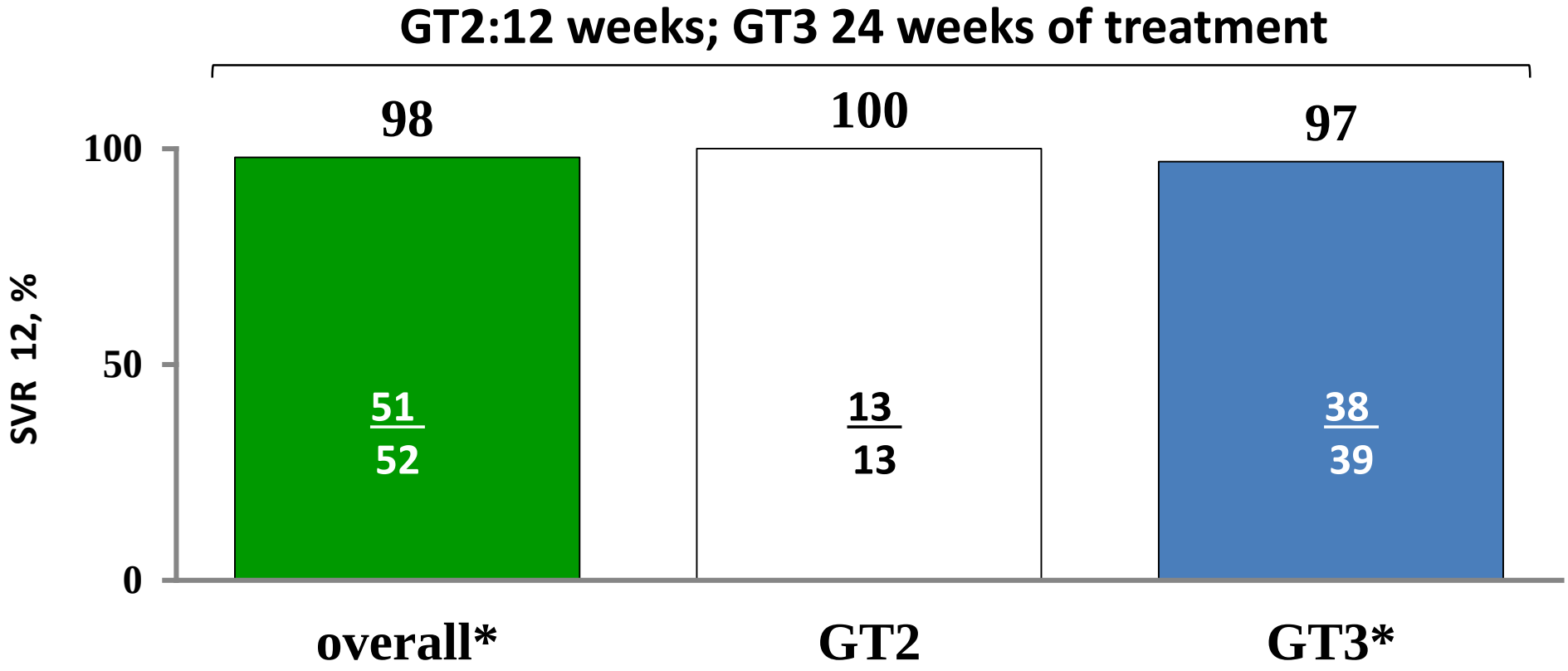
Balistreri WF, Hepatology 2017

Sofosbuvir$_{(nNS5B)}$ + ribavirin

EMA FDA

NCT 02175758, industry-drive trial

12-17 years, GT2 and 3 treatment-naïve and experienced (n 18)



***1 patient lost to follow up after achieving SVR4**

Sofosbuvir (400 mg QD) tablet, RBV weight-based.

Wirth S, Hepatology 2017

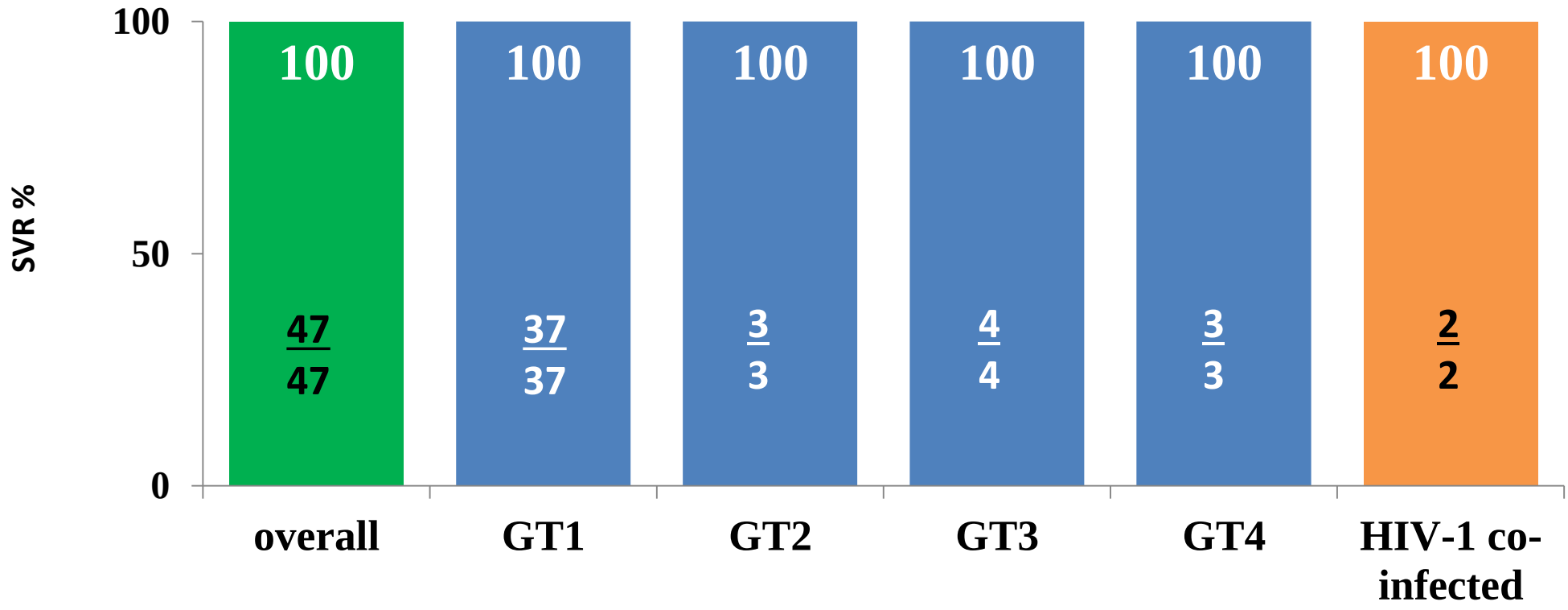
Glecaprevir(PI) / pibrentasvir(NS5A) (FDC)

EMA FDA

NCT 03067129, industry-drive trial

12-17 years, HCV GT1-6, cirrhotic and non-cirrhotic, ± HIV co-infection
DORA

non-cirrhotics 8 weeks (n 44); compensated cirrhosis 12 weeks (n 0); GT3 exp 16 weeks



Glecaprevir/pibrentasvir (300/120 mg QD), FDC

Jonas MM, Heptatology 2019

Direct Acting Antivirals

children

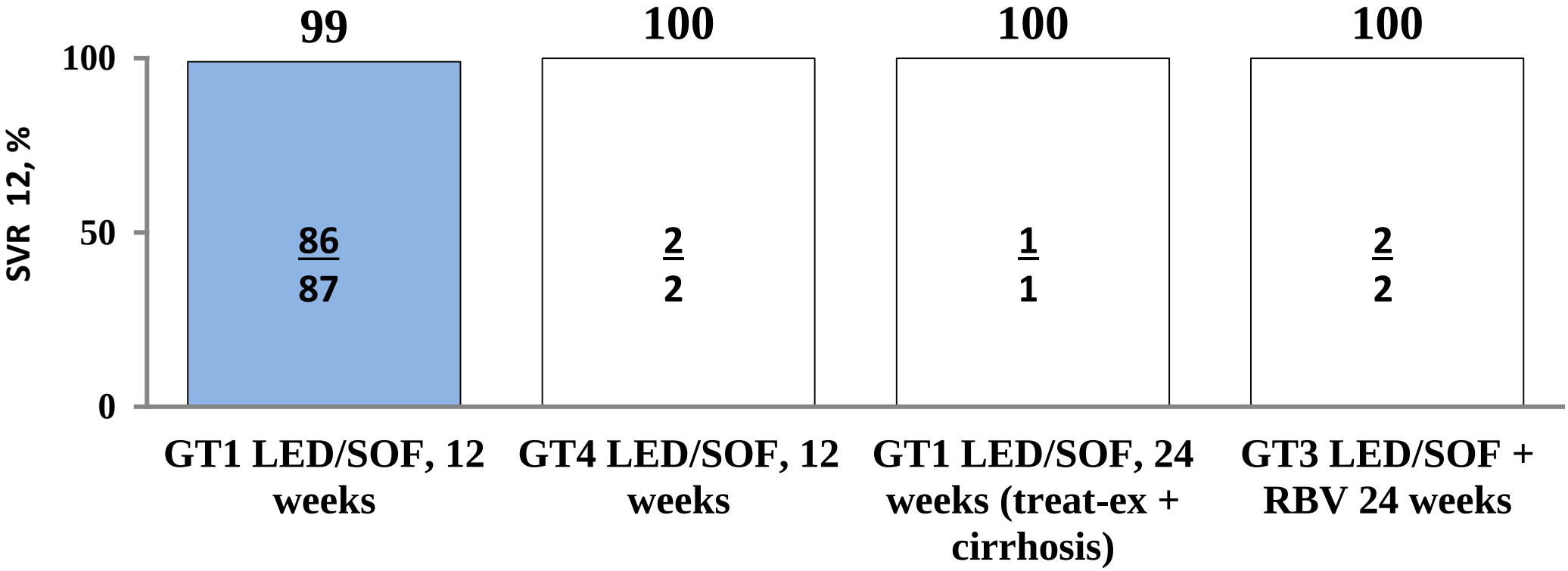
6-11 years of age

Sofosbuvir(nNS5B) / ledipasvir(NS5A) (FDC) ± ribavirin - NCT 02249182, industry-driven trial

EMA FDA

6-11 years, GT1, 3 and 4

treatment-naïve and experienced (n 20)



*1 GT1a patient with cirrhosis relapsed at follow-up 4 visit

Sofosbuvir (200 mg QD), ledipasvir (45 mg QD); **FDC tablets 22.5/100 mg**; RBV weight-based

Murray K, Hepatology 2018

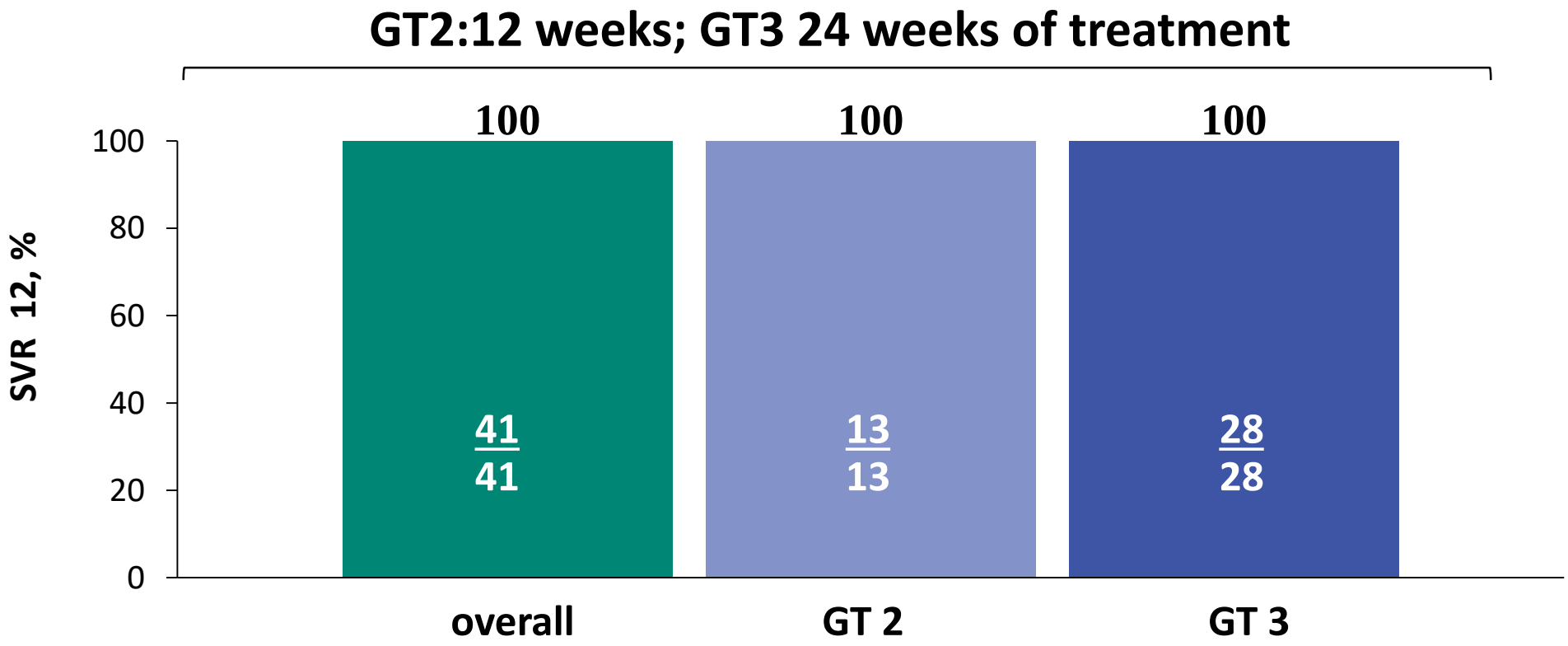
Sofosbuvir(nNS5B) + ribavirin

NCT 02175758, industry-drive trial

EMA FDA

6-11 years, GT2 and 3

treatment-naïve and experienced (n 1)



6 to <12 years old: SOF 200 mg (tablet); RBV weight-based

Rosenthal P, Hepatology 2019

Direct Acting Antivirals

children

3-5 years of age

Sofosbuvir(nNS5B) / ledipasvir(NS5A) (FDC)

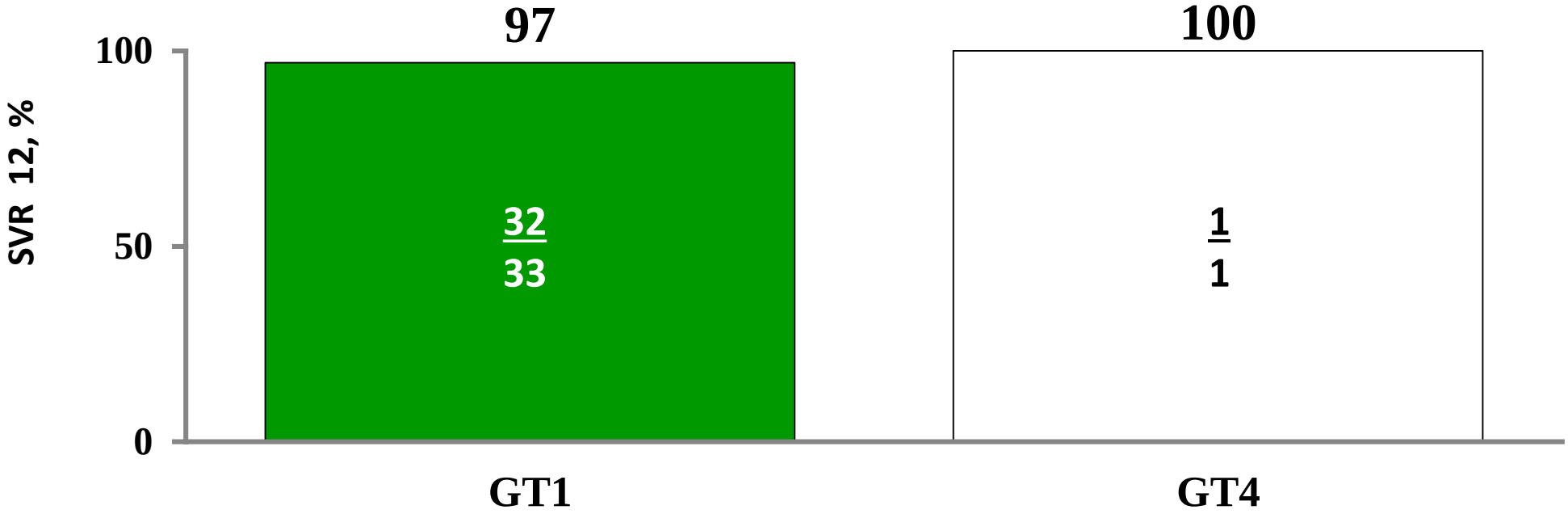
- NCT 02249182, industry-driven trial

EMA FDA

3-5 years, GT1 and 4

treatment-naïve

12 weeks of treatment



***1 GT1 3-year old patient discontinued treatment after 4 days due to abnormal drug taste and vomiting**

granules: SOF/LED 150/33.75 mg QD if < 17 Kg; 200/45 mg QD if > 17 Kg;

Schwarz KB, Hepatology 2019

Sofosbuvir$_{(nNS5B)}$ + ribavirin

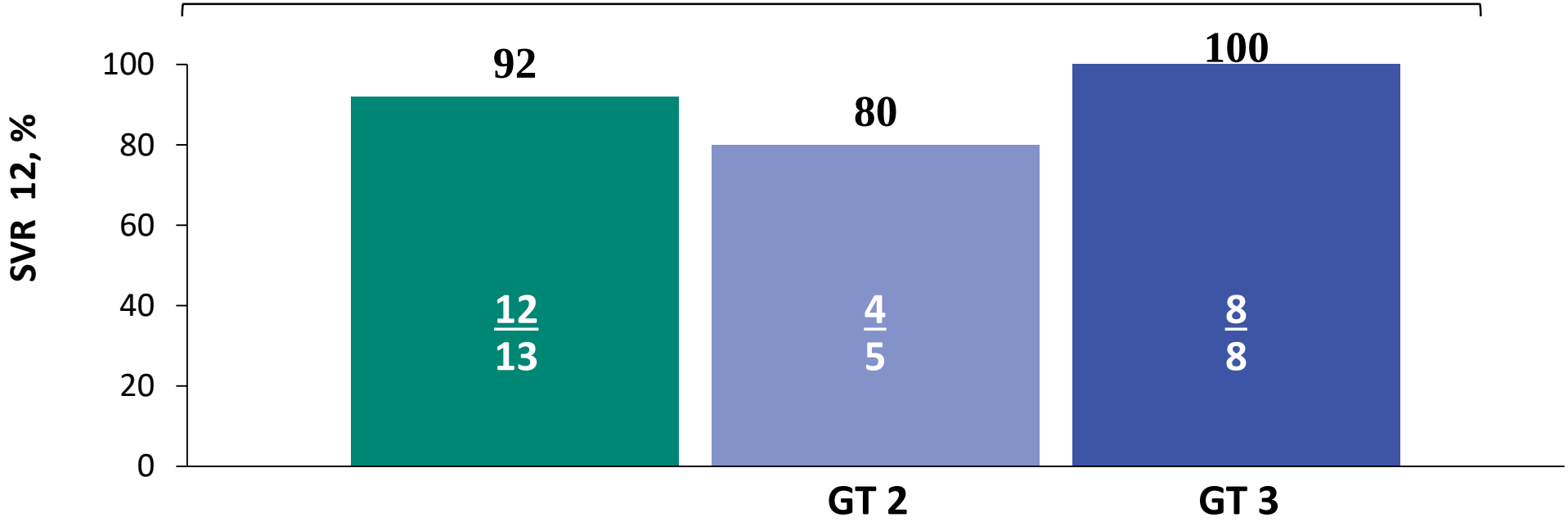
NCT 02175758, industry-drive trial

EMA FDA

3-5 years, GT2 and 3

treatment-naïve and experienced (n 1)

GT2:12 weeks; GT3 24 weeks of treatment

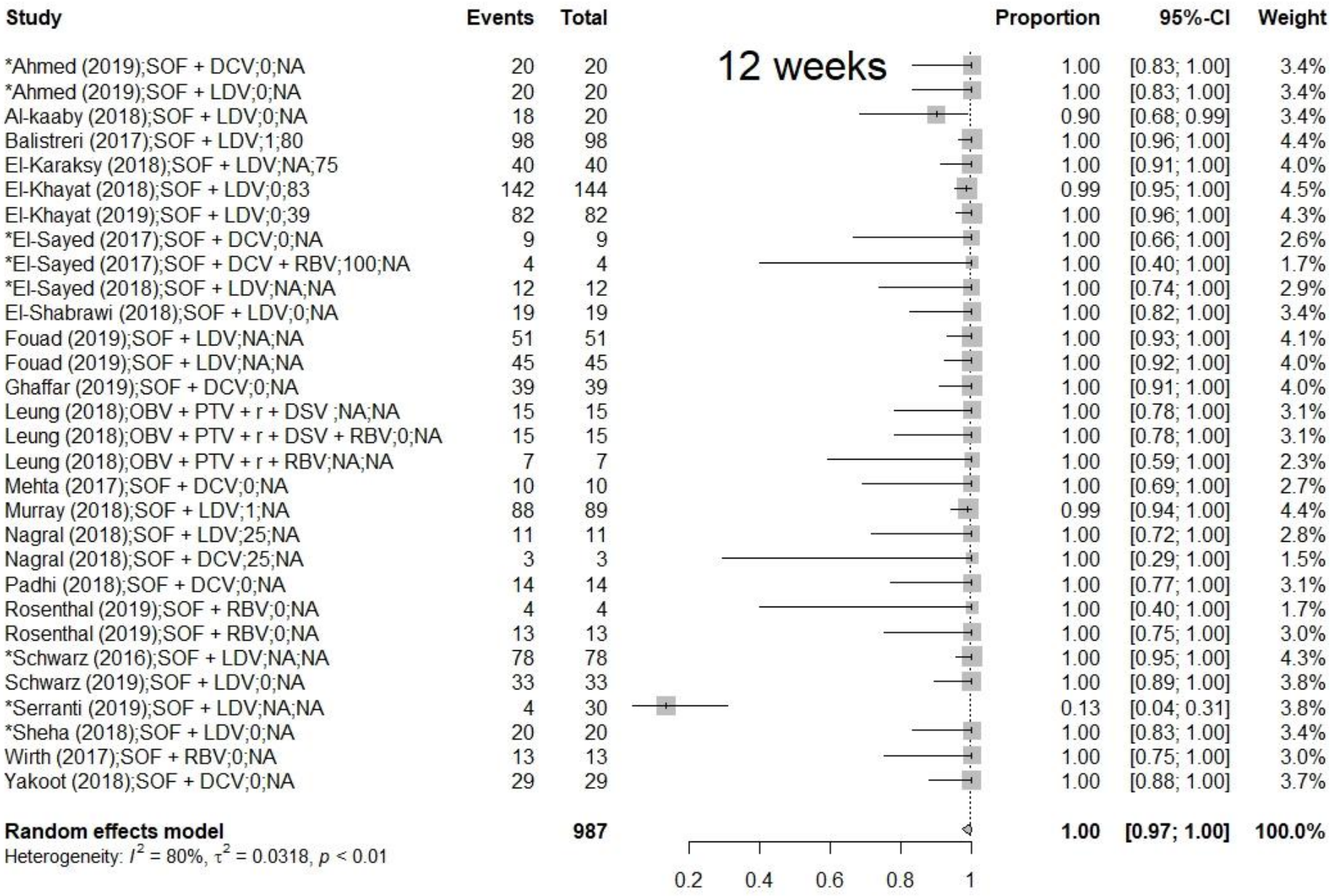


***1 GT2 4-year old patient discontinued treatment after 3 days due to abnormal drug taste and vomiting**

3 to <6 years old ≥ 17 kg: SOF 200 mg (**granules**)
3 to <6 years old < 17 kg: SOF 150 mg (**granules**); RBV weight-based

Rosenthal, Hepatology 2019

12 weeks of treatment

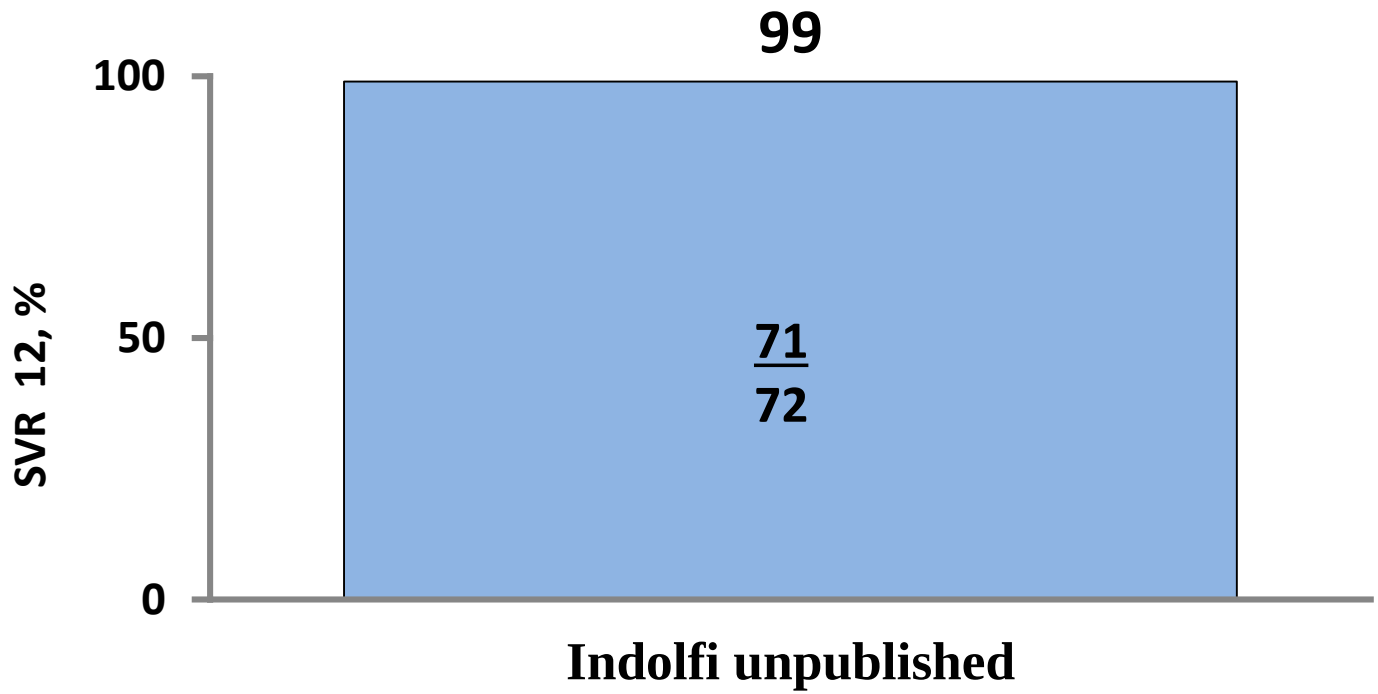


Indolfi, unpublished

Sofosbuvir(nNS5B) / ledipasvir(NS5A) (FDC)

12-17 years, Italy, CIAO-C Trial

12 weeks of treatment

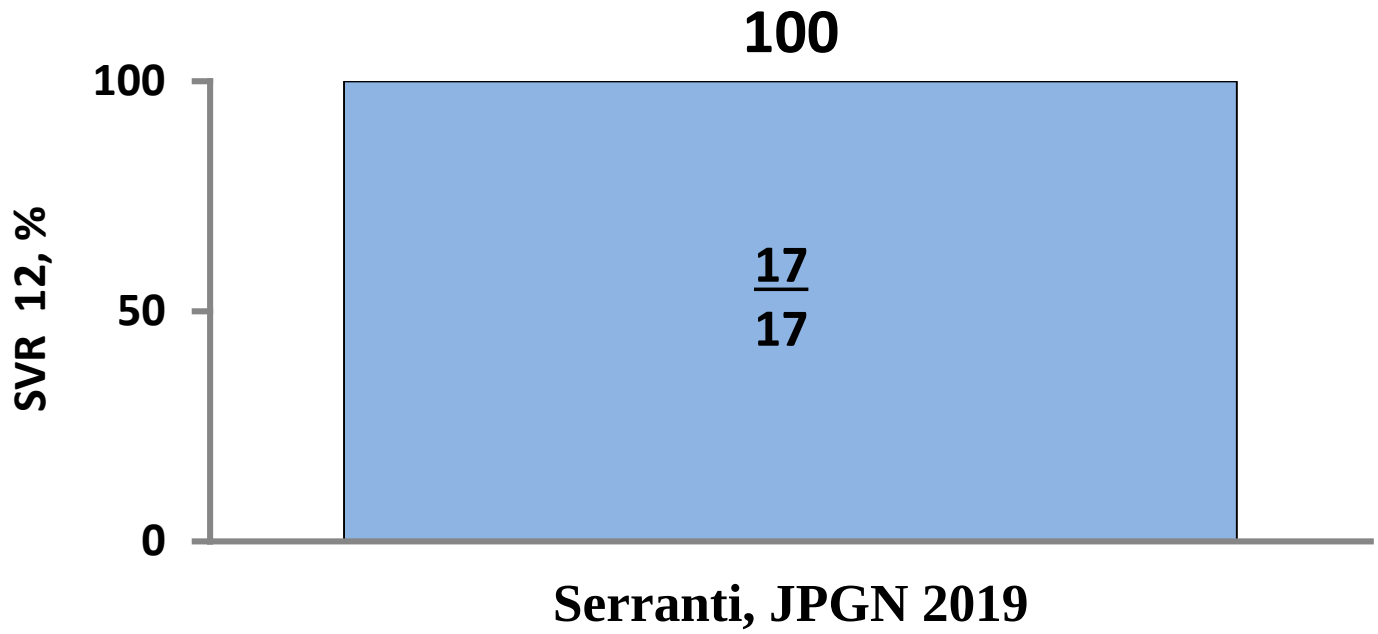


Sofosbuvir/ledipasvir (400/90 mg QD) FDC

Sofosbuvir(nNS5B) / ledipasvir(NS5A) (FDC)

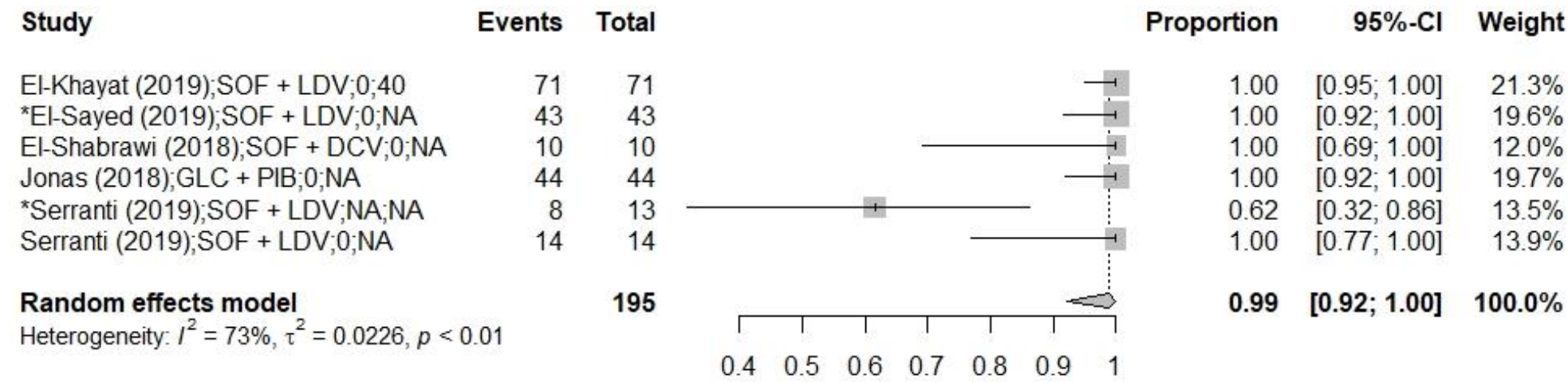
12-17 years, GT1, treatment-naïve,
HCV RNA < $6x10^6$ IU/mL (n 13)
Italy, CIAO-C Trial

8 weeks of treatment

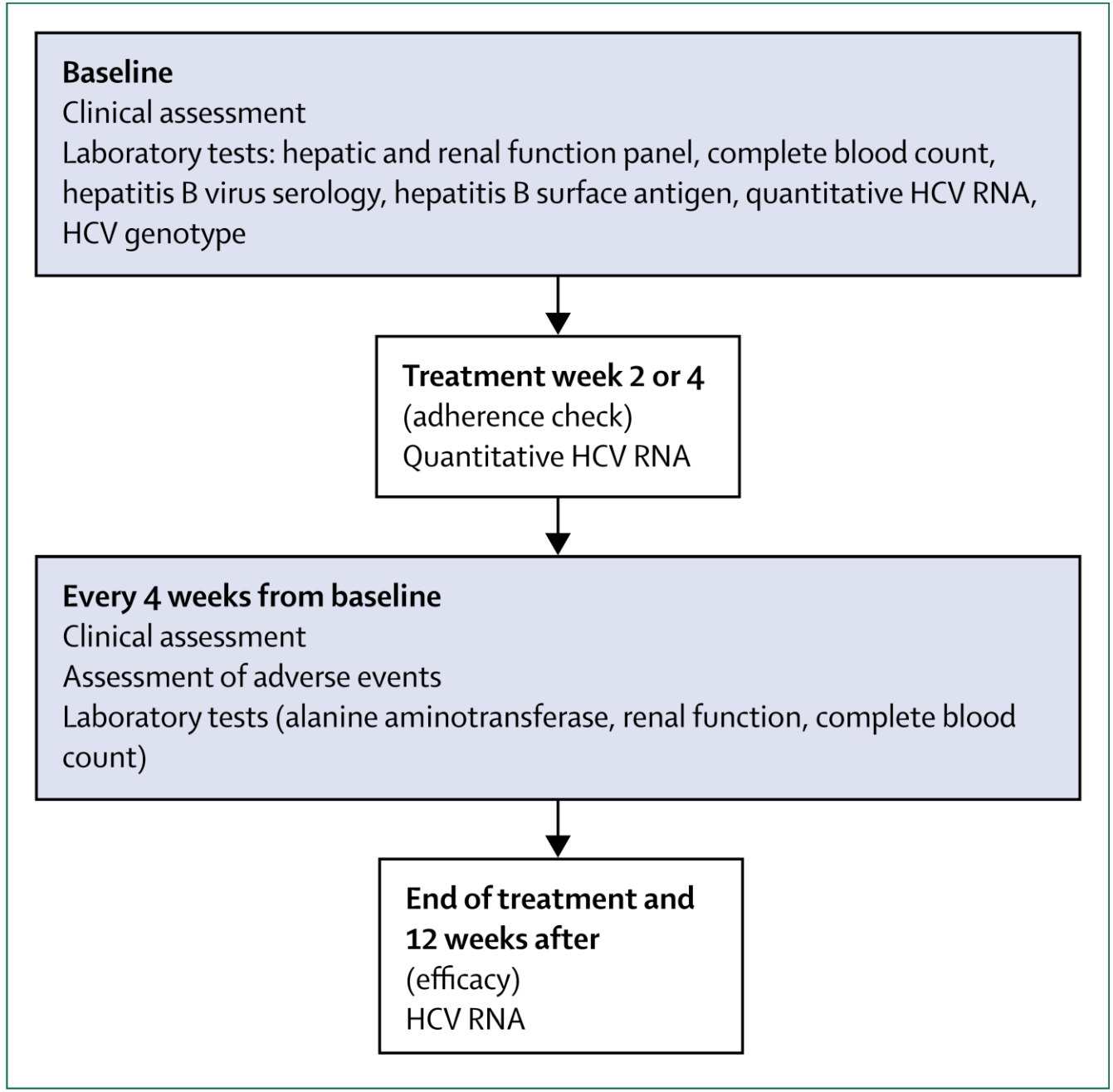


Sofosbuvir/ledipasvir (400/90 mg QD) FDC

8 weeks of treatment



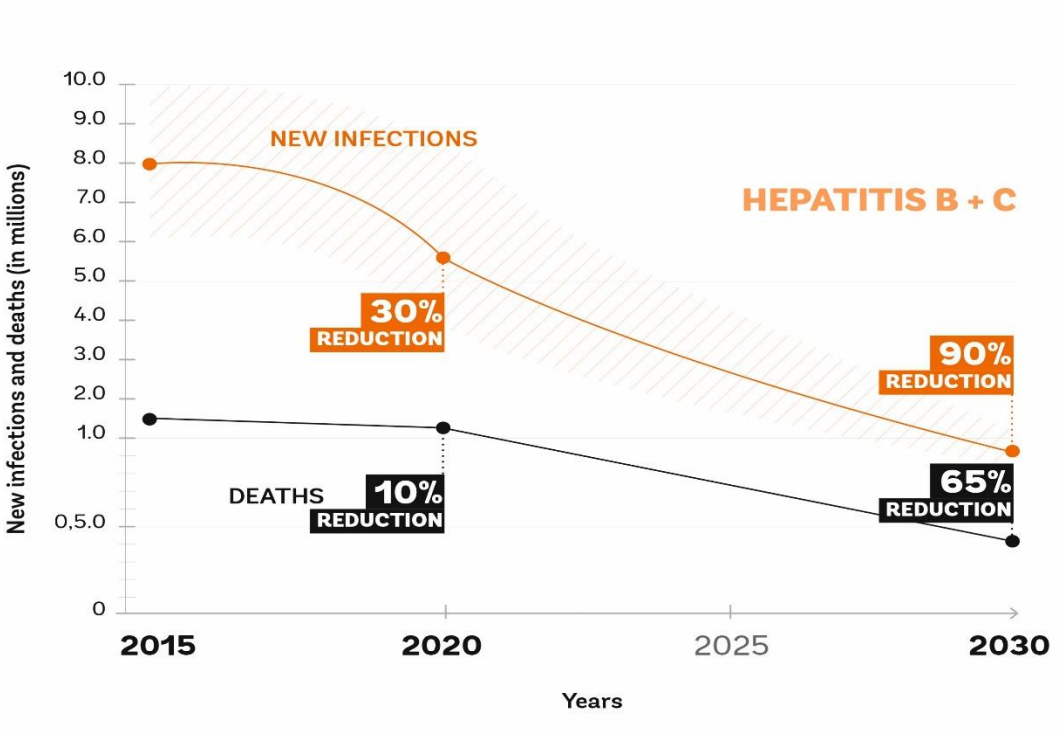
Indolfi, unpublished



Indolfi, Lancet Child & Adolesc Health 2018

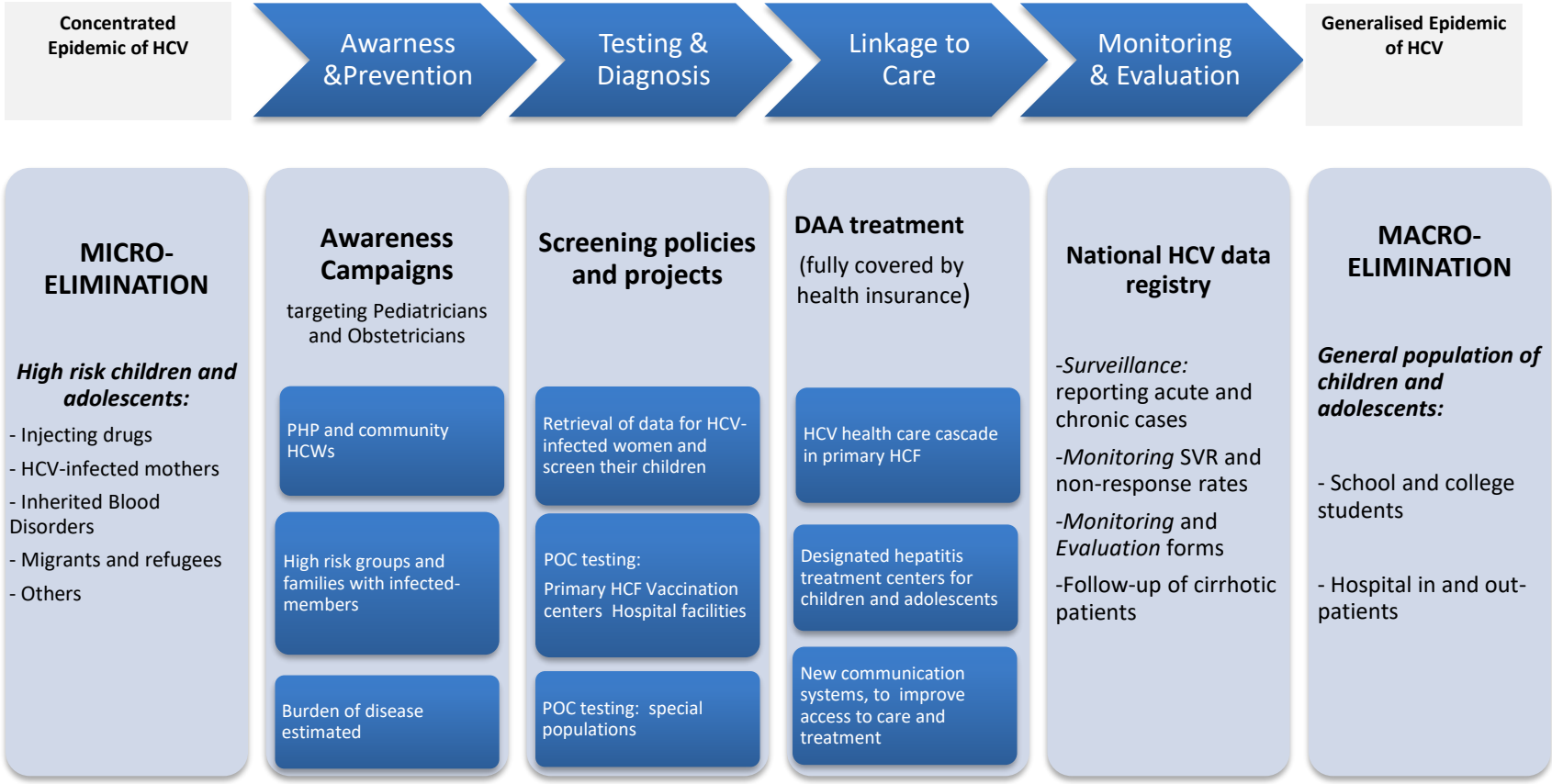
Global Viral Hepatitis Strategy – a roadmap to Elimination

Eliminate viral hepatitis as a major public health threat by 2030, as defined by:



	Interventions	Indicator	2015 baseline	Targets 2020	Targets 2030
1	Hepatitis B vaccination	HEPB3 coverage	84%	90%	90%
2	HBV PMTCT[a]	HEP vaccine birth dose coverage	39%	50%	90%
3	Blood safety	Donations screened with quality assurance	97%	95%	100%
	Injection safety	Proportion of unsafe injections	5%	0%	0%
4	Harm reduction	Syringes & needles distributed/PWID/year	27	200	300
5	Testing services	% HBV-infected diagnosed	9%	30%	90%
		% HCV-infected diagnosed	20%	30%	90%
	Treatment	% diagnosed with HBV on treatment	8%[b]	–[c]	80%[d]
		% diagnosed with HCV started on treatment	7%[b]	–[c]	80%[d]

Courtesy of Philippa Easterbrook, WHO



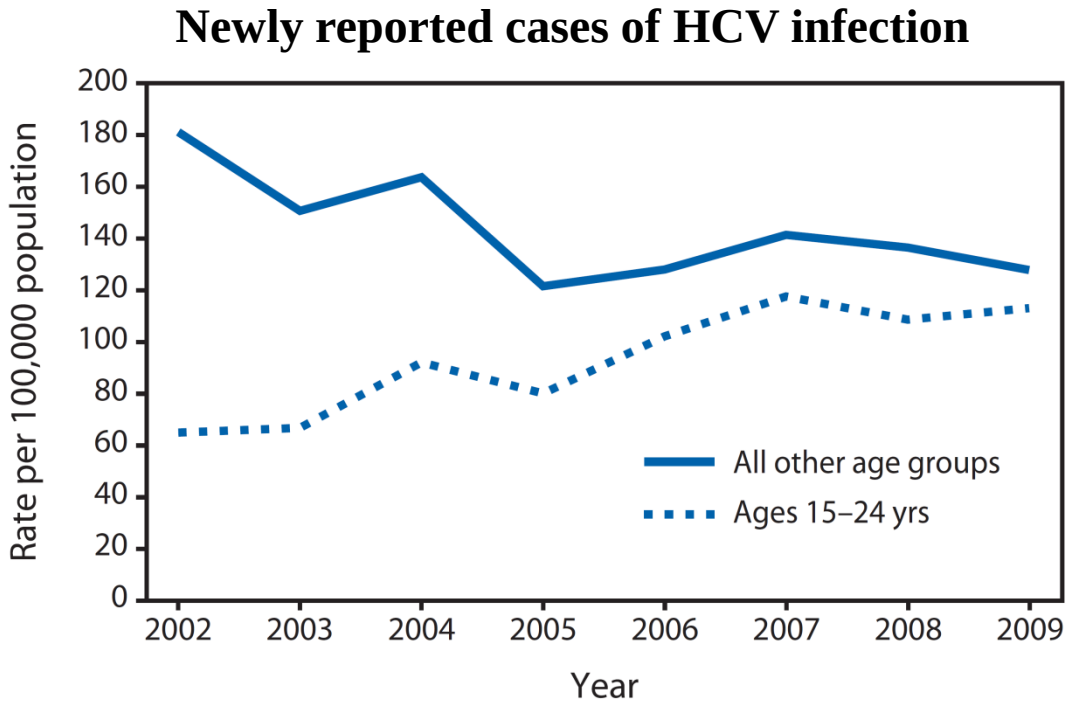
PHP, primary health care physicians; HCWs, health care workers; POC, point of care; HCF, health care facilities; DAA, direct-acting antivirals; SVR, sustained virological response.

El-Sayed & Indolfi, Seminars Liver Dis 2020

Horizontal Transmission

Raising concern

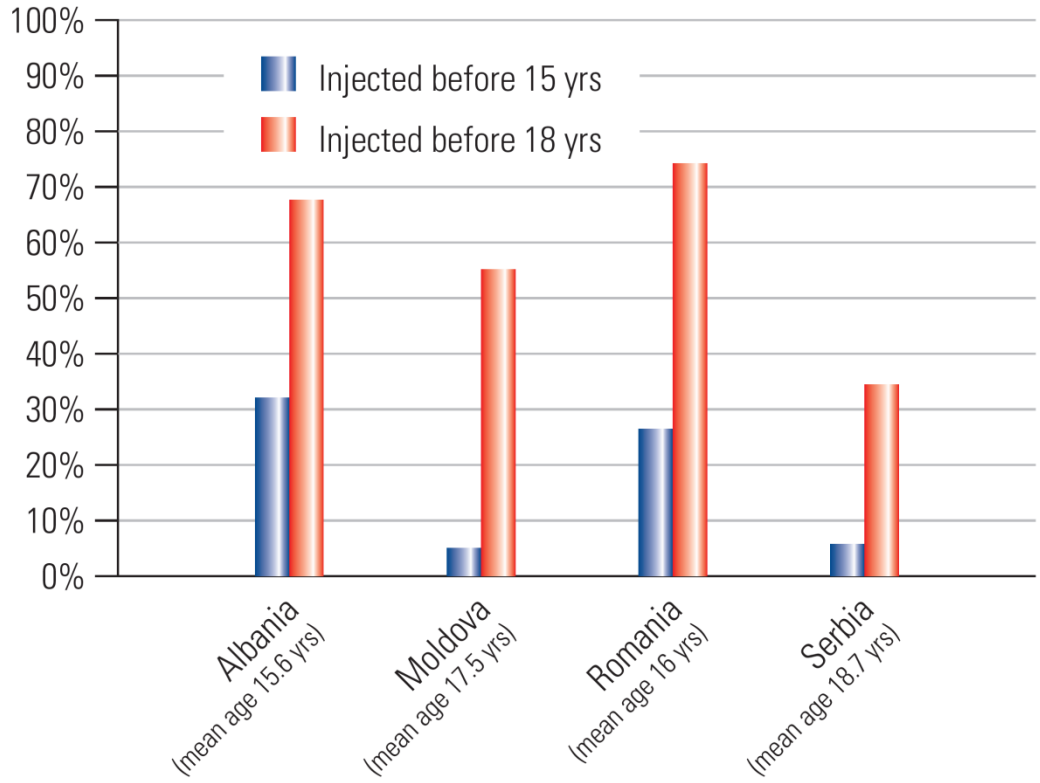
❖ **horizontal transmission** through contaminated objects such as syringes shared among injection drug users has been described in adolescents and young adults



Centers for Disease Control and Prevention, MMWR 2011

Injection Drug Use in EU Children and Adolescents

Age at first injection among injecting drug users (IDUs) aged 15–24 years



Douthwaite M, www.unfpa.org/public/iattyp/pid/5525#research
Courtesy of Claire Thorne

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Health-Related Quality of Life

Sofosbuvir + Ribavirin Study

Peds QL-4.0-SF-15 questionnaire

n 50; 14.80 ± 1.85 years

baseline

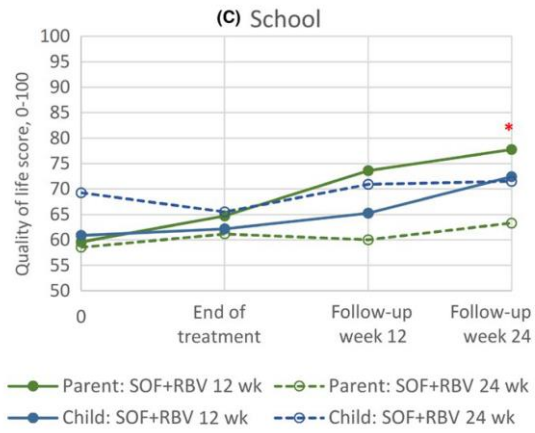
- **lower** school functioning scores

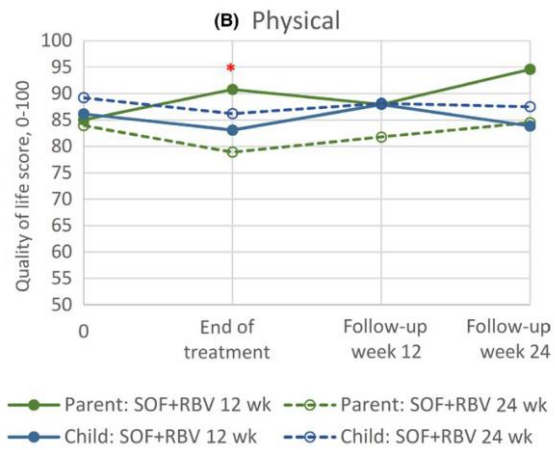
end of treatment

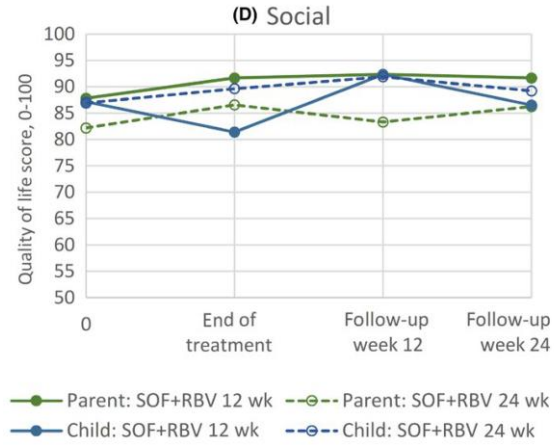
- **no decrements** in any HRQL scores

post-treatment

- **improvement** in social functioning score

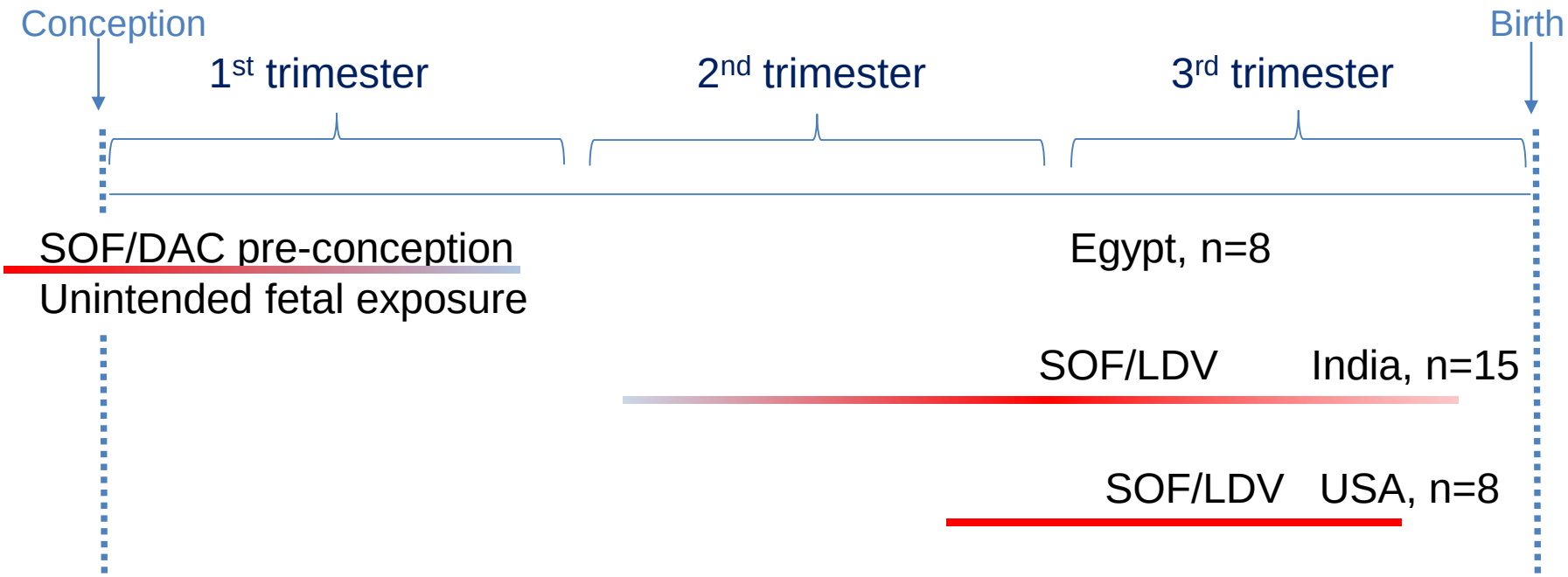






Younossi, J Viral Hep 2018

Studies of DAAs in pregnancy



El-Sayed. Abstract # THU-137. The International Liver Congress 2019.
Yattoo. Abstract # O-HCV-38. 27th Annual Conference of Asian Pacific Association for the Study of the Liver, 2018
Chappell. Abstract # 87. Conference on Retroviruses and Opportunistic Infections 2019.

Conclusions

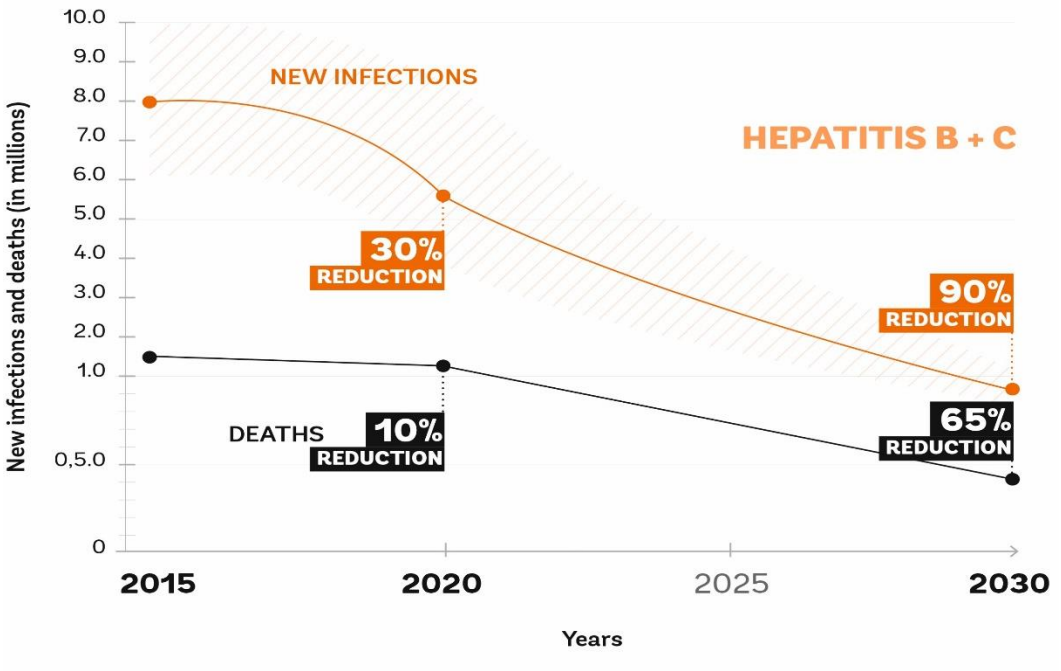
- **DAAs are effective and safe in children**

- **we should move forward toward the new concept of treating the infection instead of the disease**

- **consistency across the different society guidelines is an achievable and desirable target**

Global Viral Hepatitis Strategy – a roadmap to Elimination

Eliminate viral hepatitis as a major public health threat by 2030, as defined by:



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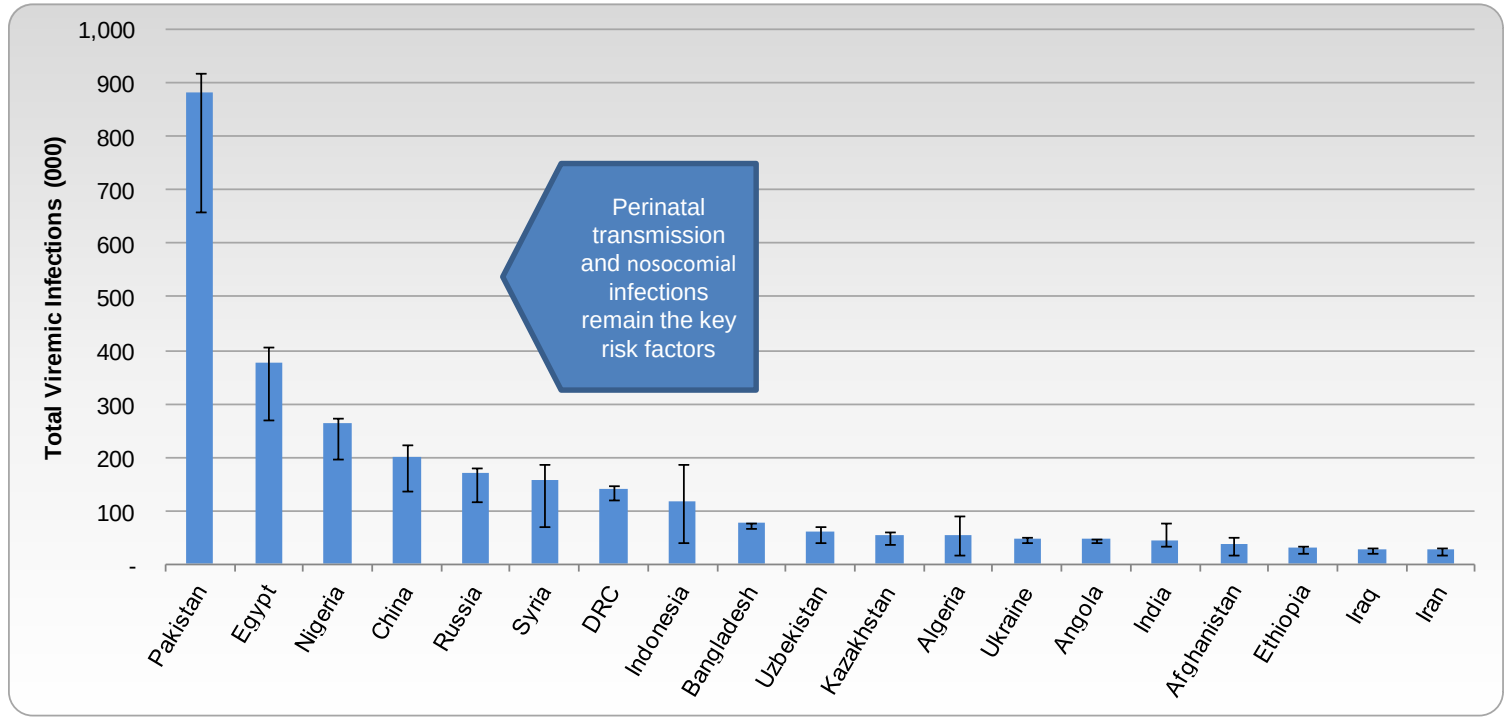
Courtesy of Philippa Easterbrook, WHO

Burden, Epidemiology and Natural History of Hepatitis C in Children



19 countries accounting for 80% of all Pediatric HCV Infections

- Globally, estimated 3.5 (3.1-3.9) million children 1- 15 years have HCV viraemic infection
- Viraemic prevalence: 0.3% in HIC and 0.6% in LIC

Source: Polaris Observatory (http://polarisobservatory.org; El-Sayed and Razavi, Global Estimate of HCV Infection in The Pediatric and Adolescent Population , (2015). P1263. J Hepatol;62:S831–S832.

Protocol Synopsis

Study Title	A Phase 2/3, Open-Label, Multicentre, Single arm, multi-cohort trial to Investigate the Pharmacokinetics, Safety, Acceptability and Efficacy of the of Sofosbuvir (SOF) in combination with Daclatasvir (DCV) in treatment-naïve, non-cirrhotic adolescents and children with Chronic HCV Infection
Sponsor	PENTA Foundation
Principal Investigator and pharmacologist	Giuseppe Indolfi Tim Cressey (Pharmacology)
Study Centers Planned	Involvement of study sites in several HCV prevalence countries is being considered: Egypt, Ukraine (with UNICEF), Mongolia, Uzbekistan, India-Punjab, Pakistan (PENTA training scheduled early 2020) and Georgia
Rationale	To achieve WHO's goals by 2030, it is pivotal to understand the current challenges associated with HCV elimination worldwide and undertake strategic efforts to overcome these challenges. In the absence of a vaccine, HCV treatment is central to infection control. In recent years, the new DAA combinations have revolutionized the treatment of chronic HCV infection globally. These treatments have excellent efficacy and safety both in adults and children with over 90% rates SVR. The few side effects, the short treatment durations (as short as 8 weeks) have dramatically improved patient adherence relative to the previous standard of care – pegylated interferon and ribavirin. Although an increasing number of DAAs have gained approval for adults since 2011 worldwide, the expansion of DAA treatment to adolescents and children and access to DAA for these populations remains slow and limited. DAA regimens are still largely unaffordable to many children and adolescents worldwide. In the context of the Global Accelerator for Paediatric Formulations (GAP-f) led by the World Health Organization, the development of a child appropriate combination of sofosbuvir and daclatasvir has been prioritized to cover the needs of children older than 3 years of age.